PATENT
ATTORNEY DOCKET NO.: 056291-5073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Confirmation No. 8999

John D.C. ROSAMUND, et al. Group Art Unit: 1645

Application No.: 10/069,062 Examiner: Padmavathi Baskar

Filed: February 21, 2002

For: PROTEIN

REQUEST FOR CORRECTED FILING RECEIPT

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Window,
Randolph Building
Alexandria, VA 22314

Sir:

Attached is a copy of the Issue Fee Transmittal paid today, December 2, 2005 in the above application for which issuance of a corrected filing receipt is respectfully requested.

The inventor's name, ROSAMOND, was inadvertently misspelled throughout the prosecution. A copy of the originally filed Declaration is attached; although the typed name is misspelled, the inventor's signature indicates and –o- in the last name, not a –u-, and said inventor neglected to correct this error by crossing out the incorrect spelling and initialing the margin. Also attached is a 132 Declaration signed by Mr. Rosamond which clearly shows the spelling of his name. The undersigned includes herewith a copy of the published International application upon which this case is based, clearly indicating ROSAMOND is the correct spelling. Issuance of a corrected Official Filing Receipt is requested in order to correct the Patent Office database, leading to correct printing on the Letters Patent.

A corrected Application Data Sheet was filed November 19, 2004, to which no response was received.

It is believed that the above correction is not due to the applicants' error; however, should the Office disagree, kindly charge any fee due to Deposit Account 50-0310.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Donald J. Bird
Reg. No: 25,323

Dated: December 2, 2005

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/14533 A3

(54) Title: PHOSPHOMEVALONATE KINASE (PMK) GENE (ERG8) FROM *CANDIDA ALBICANS*

(57) Abstract: This invention relates to polynucleotides, polypeptides encoded by these polynucleotides, to the production of such polynucleotides and polypeptides, and to the uses of such polynucleotides and polypeptides. More specifically, the invention relates to the phosphomevalonate kinase (PMK) gene (ERG8 gene) from *Candida Albicans* (*C. albicans*), to methods for its expression yielding phosphomevalonate kinase protein, to hybrid organisms for use in such expression methods, to methods for purification of the protein, to methods and tools for diagnosing *C. albicans* infection and to assays for identifying inhibitors of the enzyme which

DJB

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/069,062	02/21/2002	1645	1254	056291-5073	1	15	4

CONFIRMATION NO. 8999

09629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

FILING RECEIPT

OC000000008560041

Date Mailed: 08/05/2002

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

John David Charles Rosamond, Waltham, MA;
Norbert Friedemann Schnell, Waltham, MA;

Domestic Priority data as claimed by applicant

THIS APPLICATION IS A 371 OF PCT/GB00/03100 08/15/2000

Foreign Applications

UNITED KINGDOM 9919766.7 08/21/1999

Projected Publication Date: Not Applicable, filed prior to November 29,2000

Non-Publication Request: No

Early Publication Request: No

Title

Protein

Preliminary Class

DJB

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/069,062	John David Charles ~~Rosamund~~ Rosamond	056291-5073

INTERNATIONAL APPLICATION NO.	
PCT/GB00/03100	
I.A. FILING DATE	PRIORITY DATE
08/15/2000	08/21/1999

09629
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WASHINGTON, DC 20004

CONFIRMATION NO. 8999
371 ACCEPTANCE LETTER

OC000000008560042

Date Mailed: 08/05/2002

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.494 OR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as an Elected Office (37 CFR 1.495) , has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

02/21/2002	02/21/2002
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- U.S. Basic National Fee
- Assignee Statement
- Biochemical Sequence Diskette
- Biochemical Sequence Listing
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Information Disclosure Statements

8/13-05

- Oath or Declaration

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

TAMALA D HOLLAND
Telephone: (703) 305-5483

PART 1 - ATTORNEY/APPLICANT COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

PATENT
ATTORNEY DOCKET NO.: 056291-5073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	
	)	
ROSAMOND et al.	)	
	)	
U.S. Application No.: 10/069,062	)	Group Art Unit: 1645
	)	
Filed: February 21, 2002	)	Examiner: Baskar, P.
	)	
FOR: PROTEIN	)	

Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

DECLARATION UNDER 35 U.S.C. § 1.132
Of INVENTOR JOHN ROSAMOND

1. I am John Rosamond, currently Director of Informatics in Infection Discovery at AstraZeneca R&D Boston. I have a First Class Honours degree in Biochemistry and a D. Phil. in Microbiology from the University of Oxford, UK. I have over thirty years research experience in microbial molecular biology, genetics and biochemistry in both academic and pharmaceutical industry settings.

2. I have read the examiners report for this patent application (Article Unit 1645) from which I understand that the examiner questions whether a person skilled in the art would know how to introduce mutations into the ERG8 sequence while retaining biological activity, without excessive and undue experimental work.

3. A person skilled in the art would be able to use one of several algorithms to align the ERG8 protein sequences from *Candida albicans* (hereinafter C. albicans) and *Saccharomyces cerevisiae* (hereinafter S. cerevisiae) based on information available prior

to the filing dates associated with this application. One example of such an alignment is shown in Figure 1. From such an alignment, the person skilled in the art would be able to identify regions of contiguous sequence that are conserved in both proteins, as exemplified by the regions of the proteins shown in bold italicized text in Figure 1. The conservation of such regions or domains would be known by this person as likely to play a key role in the enzymatic activity of the protein, for example by making key contributions to the 3-dimensional structure of the active site. Consequently, a person skilled in the art would recognize that these regions were unlikely to be able to accommodate changes to the amino acid sequence without affecting the biological function.

4. From the same alignment, a person skilled in the art would recognize regions that showed less overall conservation as being those parts of the protein that could potentially accommodate mutation without loss of biological function. On the basis of published data comparing other functional homologs from C. albicans and S. cerevisiae, (for example Sherlock et al., (1994) Molecular & General Genetics 245, 716-723; Nolan & Rosamond, (1996) Gene 183, 159-165) it would be known to a person skilled in the art, that such regions are typically found at the N- and C-termini of the proteins. Analysis of the aligned ERG8 proteins (Figure 1) reveals that these proteins have relatively little identity beyond residue 385 of the C. albicans protein. This region would be seen to provide scope for deletion or a series of point mutations that would be likely to retain biological function.

5. Using the cognate DNA sequence for the ERG8 gene, the person skilled in the art would be able to design primers that could be used to amplify the ERG8 gene by PCR. The primers could be further designed to modify a specific amino-acid residue in the C-terminal region or to engineer the deletion of the residues downstream of amino acid 385. The amplified product would be ligated into a suitable plasmid vector, which would be cloned, then transformed into a strain of bacterium to express the product of the ERG8 gene. Function of the mutated ERG8 gene on the plasmid would be assessed by the ability to generate active phosphomevalonate kinase using any one of several well known

assays for detecting the change in ATP and ADP levels that represent the activity of PMK in the presence of phosphomevalonate. The specification of this application discusses these assays for PMK activity on pages 11 and 12 of the as-filed application. This would allow rapid identification of mutations in ERG8 that retained function, but which differed from the original wild-type sequence either by a single mutation, or by deletion of the non-conserved C-terminal region.

6. In addition to a gross deletion of a region of the ERG8 protein, as described above, a person skilled in the art would recognize that strains carrying multiple point mutations in the ERG8 gene could be identified rapidly either occurring naturally in clinical isolates of C. albicans as a result of natural allelic polymorphism or engineered after random mutagenesis.

7. A person skilled in the art would know that significant natural allelic variation occurs in all characterized microbial pathogens, including C. albicans (for example Miyazaki et al. (1999) Gene 236, 43-51). These natural variants contain single or multiple amino-acid changes in proteins when compared with the original reference strain, although the proteins retain biological activity as evidenced by the viability of the clinical isolates. Recognizing this, a person skilled in the art would be able to clone the ERG8 gene from any collection of clinical isolates of C. albicans using well established methods followed by the use of standard methods to determine the sequence of any one of the naturally occurring ERG8 genes, and hence the naturally occurring C. albicans ERG 8 proteins, from each clinical isolate. Comparing this sequence with the reference sequence shown in Figure 1 would rapidly identify natural variants of the ERG8 protein that, per se, will retain enzymatic activity.

8. Further, a person skilled in the art would be aware that PCR is itself mutagenic and could be used rapidly to generate multiple random variants of the C. albicans gene that could be screened for enzymatic activity. For this, such a person would design primers that would anneal to regions upstream and downstream of the ERG8 gene. These primers would be used to amplify the ERG8 gene by PCR using conditions known to

favor error-prone amplification (for example Vartanian J.P. et al. (1996) Nucleic Acids Research 24, 2627-2631). The products of the amplification would be cloned into a plasmid vector such that the gene product would be expressed in a bacterium and the activity of the resultant protein assayed using one of the methods described in the application. This would allow the rapid identification of variants of the ERG8 protein that retain enzymatic activity but which might vary from the sequence shown in Figure 1 by one or several residues.

9. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

18th November 2004
Date

John David Charles Rosamond, Ph.D.

Figure 1. Alignment of C. albicans ERG8 protein (upper) with S. cerevisiae ERG8 protein (lower). A vertical line between the sequences indicates identical amino acids. Examples of highly conserved motifs are shown in bold, italicized text.

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  3 KAFSAPGKAFLAGGYLVLEPIYDAYVTALSSRMHAVITPKGTSLKES...RIKISSPQFA 59
     |||||||| ||||||||   | | |  || |||||  | | ||  |        | ||
  5 RAFSAPGKALLAGGYLVLDTKYEAFVVGLSARMHAVAHPYG.SLQGSDKFEVRVKSKQFK 63

 60 NGEWEYHISSNTE.KPREVQSRINPFLEATIFIVLAYIQPT.EAF...DLEII.IYSDPG 113
     ||| ||||      |       ||| |  |  |  |  |         |  | | ||
 64 DGEWLYHISPKSGFIPVSIGGSKNPFIEKVIANVFSYFKPNMDDYCNRNLFVIDIFSDDA 123

114 YHSQEDTETKTSSNGEKTFLYHSRAITEVEKTGLGSSAGLVSVVATSLLSHFI...PNVI 170
    ||||||  |     |      ||  | || ||||||||||| |  | | | |     |
124 YHSQEDSVTE..HRGNRRLSFHSHRIEEVPKTGLGSSAGLVTVLTTALASFFVSDLENNV 181

171 STNKDILHNVAQIAHCYAQKKIGSGFDVATAIYGLIVYRRFQPALINDVFQVLESDPEKF 230
           || || ||| || ||||||||| | || | |||| ||||
182 DKYREVIHNLAQVAHCQAQGKIGSGFDVAAAAYGSIRYRRFPPALISNLPDI...GSATY 238

231 PTELKKLI.ESNWEFKHERCTLPYGIKLLMGDVKGGSETPKLVSRVLQWKKEKPEESSVV 289
       |  |  |  |        || |  | ||| | |||| |||  |  |      ||
239 GSKLAHLVDEEDWNITIKSNHLPSGLTLWMGDIKNGSETVKLVQKVKNWYDSHMPESLKI 298

290 YDQLNSANLQFM...KELREMREKYDSDPETYIKELDHS.........VEPLTVAIKNIR 337
    |  |  ||  ||     |    |  |         |                  |   ||
299 YTELDHANSRFMDGLSKLDRLHETHDDYSDQIFESLERNDCTCQKYPEITEVRDAVATIR 358

338 KGLQALTQKSEVPIEPDVQTQLLDRCQEIPGCVGGVVPGAGGYDAIAVLVLENQVGNFKQ 397
          |  |   ||| ||| ||| ||   |      |||||||||||     |
359 RSFRKITKESGADIEPPVQTSLLDDCQTLKGVLTCLIPGAGGYDAIAVIT..KQDVDLRA 416

398 KTLENPDYFHNVYWVDLEEQTEGVLEEK.PEDYIGL 432
     |  |   |  | | |      ||  || || |
417 QT.ANDKRFSKVQWLDVTQADWGVRKEKDPETYLDK 451
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